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Comments
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Case 35-2004: A 68-Year-Old Man with End-Stage Renal Disease and Thickening of the Skin

Samuel L. Moschella, M.D., Jonathan Kay, M.D., Bonnie T. Mackool, M.D., and Vincent Liu, M.D.

Dr. Amin Fazeli (Dermatology): A 68-year-old man was evaluated in this hospital by a dermatologist because of progressive thickening of the skin of the arms and legs.

The patient had had type 2 diabetes mellitus for 35 years, complicated by end-stage renal disease that required hemodialysis, diabetic neuropathy that resulted in leg pain and difficulty walking, chronic foot ulcers, and retinopathy; he was legally blind. He had coronary artery disease that had necessitated bypass grafting of four vessels, paroxysmal atrial fibrillation, and hypertension.

For the seven months before the evaluation, progressive thickening of the skin, particularly of the legs, had developed. He had also had weakness of the legs and had fallen at home with increasing frequency. Electromyographic studies, six months before admission, showed a severe generalized axonal sensorimotor polyneuropathy. Four months before he was admitted, examination of a skin-biopsy specimen from the leg disclosed subcutaneous fibrosis, involving both lobules and septa, with extension into the deep dermis. These symptoms were believed to be most consistent with lipodermatosclerosis, but the differential diagnosis had included nephrogenic fibrosing dermopathy. One month before admission, he visited the emergency room of another hospital, and reported frequent falls at home and weakness that had caused him to start using a walker.

Four days before the evaluation by the dermatologist, he had been admitted to this hospital because of upper gastrointestinal bleeding. For the preceding 6 to 12 months, he had had intermittent indigestion and heartburn, which were relieved by antacids. He did not have chest pain, abdominal pain, or diarrhea.

The patient was a retired firefighter. He had been living in a rehabilitation facility for the past three weeks because of his inability to walk. His medications included aspirin, insulin, docusate sodium, heparin (500 units subcutaneously, twice daily), gabapentin (100 mg, three times per week), vitamin B complex, atorvastatin, atenolol, nifedipine, isosorbide mononitrite, warfarin, and prednisolone eye drops.

The blood urea nitrogen level was 33 mg per deciliter (11.78 mmol per liter), the creatinine level 4.8 mg per deciliter (424.32 µmol per liter), the albumin level 2.6 g per
liter, the globulin level 4.4 g per deciliter, the glucose level 136 mg per deciliter (7.55 mmol per liter), and the glycosylated hemoglobin value 8.3 percent. The complete blood count, electrolyte levels, and results of liver-function tests were normal. A chest radiograph showed no pulmonary edema. Fluids were administered intravenously, and esomeprazole was given orally. Esophagogastroduodenoscopy later that day revealed esophagitis with linear ulceration and erosive gastritis, without signs of current or recent bleeding from either site. Oral esomeprazole was given twice daily. The epigastric pain and bleeding did not recur.

A dermatologist examined the patient’s skin on the fourth hospital day; among the findings were waxy, taut, hardened plaques with brown pigmentation extending from both upper thighs to the most distal point on the toes, with increasing tautness distally and from the upper arms to the fingers. These findings were most prominent over the flexures of the wrists and elbows and the area between the thenar and hypothenar prominences. There were 30-to-40-degree flexion contractures of both elbows and both knees.

A diagnostic procedure was performed.

Differential Diagnosis

Dr. Samuel L. Moschella: May we see the clinical photographs?

Dr. Bonnie T. Mackool: The skin had a brawny appearance, and the arms and legs were hyperpigmented. Large areas of the skin appeared shiny, with prominent induration extending from the upper arms to the distal fingers (Fig. 1A). The induration was most prominent on the upper arms, with areas of normal skin between smooth hardened plaques and a very gradual transition from the indurated plaques to normal skin. Flexion contractures of the fingers and the elbows were present (Fig. 1B).

There were contractures of the knees; the patient was unable to extend his legs completely (Fig. 1C). The induration was particularly prominent in the toes and feet and extended upward to the thighs, with continuous mild erythema in the lower legs and nonpitting, shiny induration on the feet (Fig. 1D). There was no hair on the legs, and the skin had a dry appearance; the distal pulses were absent. Bandages covered bilateral and symmetric oval-shaped ulcers on the heels.

Dr. Moschella: This 68-year-old man with type 2 diabetes mellitus complicated by end-stage renal disease had waxy and erythematous plaques involving both arms and legs; the most prominent involvement was in areas of flexure, with resulting contractures. Skin manifestations are associated with both end-stage renal disease and diabetes mellitus, which should be considered in the differential diagnosis (Tables 1 and 2).¹

The violaceous reticulated dermatitis associated with plaques of calcific uremic arteriopathy usually appears on the extremities and tends to form extremely painful ischemic ulcers, which when biopsied reveal calcification of vessel walls and intraleisonal deposition of fibrin.² Porphyria cutanea tarda may produce fragility of the skin, with the formation of blisters and milia on exposed areas and sclerotic patches that are clinically and histologically consistent with morphea, hypertrichosis of the face, and peri orbital erythema.³ None of these changes were seen in this patient.

Scleredema diabeticorum is characterized by thickened skin that appears waxy and by limited joint mobility and sclerodactyly (Table 2).² Dramatic induration of the skin of the neck and upper back, and less severe induration of the chest, face, and extremities, which may affect joint mobility, are due to glycosaminoglycan deposition. Systemic involvement, such as that seen with serositis, can occur. This condition can be ruled out in this case because of the distribution of the cutaneous eruption, the lack of systemic involvement, and the histopathological features of the biopsy specimen. The signs of necrobiosis lipoidica diabeticorum are well-circumscribed, waxy, yellow-to-brown, initially indurated and later atrophic plaques on the legs, with raised red telangiectatic borders, and the presence of characteristic palisading granulomas on histopathological examination.

Lipodermatosclerosis

An initial biopsy specimen of the skin of this patient’s leg was interpreted histopathologically as consistent with lipodermatosclerosis³; however, the differential diagnosis includes nephrogenic fibrosing dermopathy. Lipodermatosclerosis usually affects women who have venous insufficiency and stasis. It is characterized by well-circumscribed, indurated, inflamed, hyperpigmented plaques of the lower part of the legs with the subsequent physical appearance of an inverted champagne bottle. Lipodermatosclerosis is characterized by the histologic changes seen in stasis dermatitis, ischemic fat necrosis, and later progressive septal fibrosis and...
obliteration of the fat lobules. The clinical and histopathological features of this case are not those of lipodermatosclerosis.

**NEPHROGENIC FIBROSING DERMOPATHY**

Cowper et al. described 14 patients with renal failure in whom a cutaneous disease similar to scleromyxedema developed; most had undergone hemodialysis, but some had not. The distribution and nature of the lesions, the absence of a paraproteinemla and visceral involvement, the presence of sclerodactyly and contractures, and the fibroblastic histopathological picture led the investigators to call this new entity nephrogenic fibrosing dermopathy. Recently, Ting et al. reported a case with systemic involvement. Forty-nine cases have been reported to the Centers for Disease Control and Prevention. The disorder has occurred in patients receiving peritoneal dialysis and in a few patients who have renal insufficiency but who have never undergone dialysis.

Nephrogenic fibrosing dermopathy is characterized by diffuse, cutaneous, hyperpigmented, brawny...
The eruptions usually start on the extremities, especially the lower legs, extend to the trunk, and rarely involve the face. Yellowish palmar papules and yellow nodules of sclera have been seen. Pruritus, burning sensations, and pain in the skin lesions have been described.

The cause of nephrogenic fibrosing dermopathy is unknown. No infectious agents, drugs, or environmental toxins have been implicated as possible agents, despite comprehensive studies. Investigation of the materials used in hemodialysis, peritoneal dialysis, and transplantation have provided no clues. The roles of high-flux dialysis and marked volume overloading are being investigated.

This patient’s clinical history and skin lesions are typical of nephrogenic fibrosing dermopathy. However, the differential diagnosis includes other conditions that are characterized by dermal and subcutaneous fibroplasias with or without sclerodactyly, and mucin deposition, or the presence of dermal, subcutaneous, and musculoskeletal amyloid deposits (Table 3).

**DIFFERENTIAL DIAGNOSIS OF NEPHROGENIC FIBROSING DERMOPATHY**

Scleromyxedema is a chronic idiopathic disorder that produces indurated plaques, nodules, and papules that contain dermal mucin and a variable degree of fibrosis. These patients do not have thyroid disease. Leonine facies and paronychial or auricular papular components may be present. Patients with scleromyxedema may also have systemic symptoms, especially of the central nervous system or cardiac system, such as paraproteinemia, elevated levels of muscle enzymes, and, rarely, myelodysplasia. The absence of lesions on the face, neck, and hands; the marked visceral involvement or paraproteinemia; and the histopathological features in this case argue against this diagnosis.

Other disorders to be considered are morphea (localized scleroderma), systemic sclerosis (scleroderma), eosinophilic fasciitis, and the eosinophilia–myalgia syndrome. Morphea is characterized by ivory-colored, localized linear or generalized plaques with violaceous borders; these plaques are examined histologically, homogenized bundles of collagen are evident, with the absence of mucin. When these lesions affect the extremities, especially in a linear fashion, they may mimic nephrogenic fibrosing dermopathy. However, unlike those of nephrogenic fibrosing dermopathy, these lesions have an erythematous border; they are white, not waxy, in appearance, and they have a characteristic histopathological picture of homogenized collagen with the absence of mucin.

Systemic sclerosis, because of the thick, tight skin, acrosclerotic changes, and associated pigmentation, can appear similar to nephrogenic fibrosing dermopathy. However, on closer inspection, there is involvement of the face (pinched facies) and telangiectatic mats, which can also appear on the hands and face. The patients with this disorder may also have the changes in the distal digital pulp associated with Raynaud’s phenomenon. Visceral involvement, especially of the gastrointestinal tract, lung, and kidneys, may occur. Such patients will have autoantibodies. No systemic changes or autoantibodies were present in this case.

Patients with eosinophilic fasciitis can have a woody induration of the distal extremities and con-
tractures, with a loss of mobility. However, they will have an elevated erythrocyte sedimentation rate, hypergammaglobulinemia, a peripheral-blood eosinophilia, and a deep-skin biopsy specimen will show thickening of the deep fascia and the presence of a patchy infiltrate of lymphocytes, plasma cells, and especially eosinophils. In a documented incident, a separate disease called the eosinophilia–myalgia syndrome developed in patients who ingested a contaminated tryptophan; this syndrome is characterized initially by fever and a generalized morbilliform eruption and later by a sclerodermoid eruption primarily confined to the extremities; a peripheral myopathy and neuropathy; and eosinophilia and elevated levels of muscle enzymes. Other than the sclerodermoid changes, none of the above features were present in this patient.

**Table 3. Clinical and Histologic Features of Nephrogenic Fibrosing Dermopathy as Compared with Disorders That Appear Similar.**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Distribution of Lesions</th>
<th>Clinical Morphologic Features of Lesions</th>
<th>Histopathological Features of Lesions</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrogenic fibrosing dermatopathy</td>
<td>Legs, feet, toes, arms, hands, fingers</td>
<td>Indurated plaques with pigmentation; sclerodactyly</td>
<td>Dermal spindle-cell proliferation (CD34+) with variable mucin deposition and little inflammation; occasional multinucleated giant cells, elongated elastic fibers, and dystrophic calcification</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Scleromyxedema</td>
<td>Face, neck, ears, fingers</td>
<td>Plaques, nodules, papules</td>
<td>Dermal fibrosis, increased mucin (often “pools”), lymphoplasmacellular infiltrate</td>
<td>Central nervous system, cardiac involvement; paraproteinemia</td>
</tr>
<tr>
<td>Morphea</td>
<td></td>
<td>Ivory-colored, localized, linear plaques, erythematous border</td>
<td>Homogenized collagen; mucin not increased</td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis (scleroderma)</td>
<td>Face, neck, arms, legs, feet, hands</td>
<td>Thick, tight skin, pigmentation, telangiectases; sclerodactyly with loss of digital pulp</td>
<td>Homogenized, thickened collagen; mucin not increased; variable inflammatory infiltrate</td>
<td>Gastrointestinal, renal, lung disease; Raynaud’s phenomenon; serology</td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
<td>Arms, legs, feet, hands</td>
<td>Woody induration, contractures</td>
<td>Fibrosis, lymphocytes, plasma cells, eosinophils</td>
<td>Elevated erythrocyte sedimentation rate, hypergammaglobulinemia, eosinophilia</td>
</tr>
<tr>
<td>Eosinophilia–myalgia syndrome</td>
<td>Generalized (morbilliform rash); arms, legs, feet, hands (scleroderma-like)</td>
<td>Morbilliform rash; scleroderma-like foci</td>
<td>Mixed inflammatory infiltrate with eosinophils</td>
<td>Ingestion of tryptophan, myopathy, neuropathy, eosinophilia, elevated levels of muscle enzymes</td>
</tr>
<tr>
<td>Fibroblastic rheumatism</td>
<td>Fingers, elbows, knees</td>
<td>Flesh-colored or erythematous nodules</td>
<td>Myofibroblastic proliferation, often with some degree of inflammation</td>
<td>Fever, polyarthritides, Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Beta_2-microglobulin amyloidosis</td>
<td>Shoulders, carpal tunnels, flexor tendons of hands; tongue (macroglossia)</td>
<td>Periarticular thickening (shoulder pad); cutaneous papules (rare), nodules</td>
<td>Amyloid deposition</td>
<td>Chronic renal failure</td>
</tr>
</tbody>
</table>

**DIAGNOSTIC PROCEDURE**

To confirm the diagnosis in patients with nephrogenic fibrosing dermopathy, the biopsy should be performed on a firm nodular or plaque lesion on the lower leg, preferably the anterior thigh if it is involved, because in such a location it would be easier to take a deeper biopsy specimen, to close the biopsy site, and to minimize the danger of dehiscence.

*Dr. Nancy Lee Harris (Pathology): Dr. Kay, would you please review the differential diagnosis in this case, from your perspective as the rheumatology consultant?*

*Dr. Jonathan Kay: Two features of this patient’s condition prompted rheumatologic consultation: the scleroderma-like thickening of his skin and the disabling flexion contractures of his fingers, el-*
brows, and knees. I will address the differential diagnosis of his joint contractures.

Joint contracture is defined as the limitation of passive range of joint motion by structural changes of soft tissues. Skin tightening, ligament or tendon shortening, and imbalanced muscle contraction can each produce joint contractures. These changes may result from congenital abnormalities, trauma, prolonged immobilization, nerve injury, or other disorders involving skin, muscle, tendons, or ligaments.

The clinical history is sufficient to rule out congenital syndromes, trauma, or prolonged immobilization as the cause in this case. The primary symptom of peripheral neuropathy in this patient was a sensory loss without a motor component, which consequently appears to be unlikely to contribute to his flexion contractures. Physical examination showed no imbalanced muscle contractions. Fibroblastic rheumatism is an uncommon syndrome characterized by sclerodactyly, multiple cutaneous nodules, and an inflammatory polyarthritis, the joint distribution of which is similar to that of rheumatoid arthritis except for the additional prominent involvement of the distal interphalangeal joints of the hands. Patients may have flexion contractures of the fingers. This patient had no history of inflammatory polyarthritis.

Patients with diffuse systemic sclerosis (scleroderma) may have flexion contractures, most often involving the fingers and elbows but also occasionally the knees. Cutaneous thickening accounts for much of the limited joint motion observed in patients with scleroderma. However, flexion contractures of the fingers also may result from musculotendinous shortening caused by fibrosis of the flexor digitorum superficialis and profundus muscles of the forearm. This patient had no clinical features to suggest systemic sclerosis.

In patients with chronic renal failure who have received long-term hemodialysis, shoulder periarthritis, carpal tunnel syndrome, and flexion contractures of the fingers may also develop as manifestations of beta-2-microglobulin amyloidosis. The flexion contractures of the fingers are caused by amyloid infiltration of the flexor tendons, causing the tendons to adhere to one another and producing functional shortening. However, beta-2-microglobulin amyloidosis is not associated with sclerosis of the overlying skin. This patient reported no shoulder pain and did not have either soft-tissue fullness about his wrists or carpal tunnel syndrome.

Diabetic cheiroarthropathy develops in some people with diabetes mellitus and is associated with thickening of the skin over the fingers and dorsum of the hands and limited joint mobility. The digital sclerosis is often associated with flexion contractures of the interphalangeal and metacarpophalangeal joints of the hands. Flexion contractures of larger joints, such as the elbows, shoulders, and knees, may also develop. The prevalence of adhesive shoulder capsulitis, palmar flexion or tenosynovitis of the hands, and Dupuytren’s disease is substantially greater in diabetic patients than in others. Although these conditions are more common in people with type 1 diabetes than in those with type 2 diabetes, this difference is related to the increased prevalence of these syndromes with longer duration of diabetes. Patients with diabetes who have shoulder and hand disorders are more likely to have retinopathy, nephropathy, or neuropathy than are patients with diabetes who do not have these disorders.

I believe that this patient’s joint contractures were attributable to nephrogenic fibrosing dermopathy, caused by the thickened skin overlying his fingers, elbows, and knees. Diabetic cheiroarthropathy might have been a contributing factor. There did not appear to be sufficient abnormality of the joints themselves to explain his limited joint mobility.

Dr. Harris: Dr. Mackool, as the dermatologist who evaluated this patient, would you give us your clinical impressions?

Dr. Mackool: Nephrogenic fibrosing dermopathy was the working diagnosis. The skipped areas of induration with smooth transition to indurated plaques and hyperpigmentation all supported this diagnosis. I considered systemic sclerosis because of the severe woody induration on the feet, but other cutaneous and systemic manifestations of scleroderma were absent. I considered calciphylaxis, but the plaques were not painful, and over the eight months of progressive disease, purpura and ulceration, which are features of advanced calciphylaxis, did not develop. I also considered scleredema diabeticorum, but the shininess of the skin and the lack of involvement of the back, shoulders, and neck rendered this diagnosis unlikely.

Skin-punch biopsies of affected areas of the right lower leg and left anterior thigh were performed.
The specimens from the punch biopsies of skin from the two sites showed similar changes. On low-magnification scanning of the specimen taken from the left anterior thigh, there is mild hypercellularity of the dermis (Fig. 2A). Higher magnification shows a spindle-cell proliferation intercalated among the compact, clefted dermal collagen bundles that extends down through the subcutaneous fat (Fig. 2B). Mucin deposition is shown on the colloidal iron stain as blue staining in the superficial dermis (Fig. 2C). On van Gieson’s staining, elongated elastic fibers are highlighted in the superficial dermis (Fig. 2D). Immunohistochemical staining with antibodies to CD34 revealed staining of the fibroblast-like cells (Fig. 2E). In summary, the skin-biopsy specimens showed a CD34-expressing, dermal fibrocytic spindle-cell proliferation with extension into the subcutaneous fat, a slight increase in interstitial mucin, and a subtle increase in elongated elastic fibers with elastolysis.

The original definition of nephrogenic fibrosing dermopathy included dermal fibroplasia with little inflammation and mucin deposition, all of which were observed in this case. Prominent elongated elastic fibers, as seen in this case, have been described in subsequent reports of nephrogenic fibrosing dermopathy. Multinucleated giant cells and dystrophic calcification have also been reported.

The histologic differential diagnosis includes other fibrotic cutaneous disorders (Table 3), primarily scleromyxedema. Scleromyxedema is generally characterized by a lymphoplasmacellular infiltrate and prominent mucin deposition that can aggregate into pools. Morphea differs from nephrogenic fibrosing dermopathy principally in the lack of a spindle-cell proliferation. Lipodermatosclerosis classically displays so-called lipomembranous changes, characterized by microcysts lined by eosinophilic, amorphous material forming pseudopapillae. In the clinical context, the histological features in this case best fit with nephrogenic fibrosing dermopathy.

Dr. Liu: There are some histologic similarities, such as the superficial fibrosis that extends into the deep panniculus, as well as some subtle stasis changes that are characteristic of the lower leg, though true lipomembranous change was absent. Clinicopathological correlation is essential for the diagnosis of this entity.

Dr. Kay: There is no effective treatment for nephrogenic fibrosing dermopathy. Physical therapy should be initiated to maintain and attempt to improve the range of motion of contracted joints. The hands may be splinted in a functional position to prevent progression of the contractures of the finger joints. Various medical therapies have been ineffective, including topical steroids, selective H2-receptor antagonists, cyclosporine, prednisone, immunosuppressive therapy, and photopheresis. Recently, improvement was reported after plasmapheresis in three patients. Thalidomide, an inhibitor of angiogenesis and of tumor necrotic factor-α production, has been administered to several patients. My colleagues and I have observed some softening of skin in three patients treated with thalidomide. However, other patients have not improved. We recommended physical therapy and thalidomide for this patient.

Dr. Axelrod: Dr. Axelrod, as this patient’s physician, would you tell us the subsequent management of his disease and the outcome?

Dr. Kay: As Dr. Kay suggested, we treated his nephrogenic fibrosing dermopathy with thalidomide and physical therapy. Both the patient and his wife noted a gradual decrease in the firmness of the skin of the lower extremities and an increase in the range of motion of the knees, but this was insufficient to enable him to walk. His last admission, two months before he died, was instructive. Dr. Kay, would you tell us about the subsequent management of his disease and the outcome?

Dr. Kay: As Dr. Kay suggested, we treated his nephrogenic fibrosing dermopathy with thalidomide and physical therapy. Both the patient and his wife noted a gradual decrease in the firmness of the skin of the lower extremities and an increase in the range of motion of the knees, but this was insufficient to enable him to walk. His last admission, two months before he died, was instructive.
revealed bilateral pleural effusions and ascites, although his weight was unchanged and he did not have pitting edema. We concluded that the nephrogenic fibrosing dermopathy had led all of his physicians to underestimate the degree of fluid overload; the stiffness of his skin prevented the occurrence of pitting edema of the lower extremities. Tissue loss due to his enforced immobility, muscle wasting, and reduced oral intake had offset the weight gain that resulted from increased total body fluid. He underwent dialysis and the excess fluid was removed, with an ensuing reduction in weight of 17 kg. This treatment resolved his cough and improved his overall sense of well-being, his mental alertness, and his vigor. The patient died six months after the admission described.

A Physician: Is there any correlation between the duration or severity of the renal disease and the development of nephrogenic fibrosing dermopathy?

Dr. Kay: The occurrence of nephrogenic fibrosing dermopathy does not correlate directly with the duration or severity of renal disease. Unlike beta2-microglobulin amyloidosis, which typically appears five to eight years after the initiation of hemodialysis, nephrogenic fibrosing dermopathy may develop after only a short period of hemodialysis.

Nephrogenic fibrosing dermopathy.

Figure 2. Biopsy Specimen of the Skin of the Anterior Thigh.
The dermis is hypercellular (Panel A, hematoxylin and eosin), with little inflammation. A spindle-cell proliferation intercalates around clefted dermal collagen bundles (Panel B, hematoxylin and eosin). Interstitial mucin deposition is present in the superficial dermis (Panel C), seen as blue material (colloidal iron stain). Prominent elastic fibers interweave among dermal collagen bundles (Panel D, van Gieson’s stain). The dermal fibrocytic population expresses CD34 (Panel E, immunoperoxidase stain).

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